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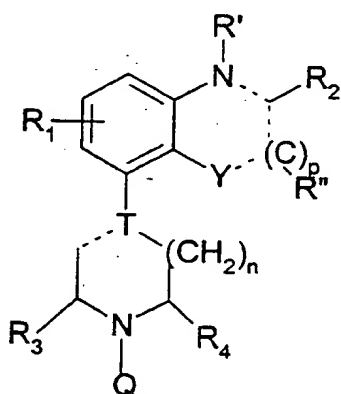
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(54) Piperazine and piperidine derivatives as 5-HT₁ receptor agonists

(57) The invention relates to a group of novel piperazine and piperidine derivatives having interesting pharmacological properties.

The compounds have the general formula (a)



(a)

wherein

- R₁ is hydrogen or fluoro,
- R' is H or C₁₋₄-alkyl,
- R₂ is H, C₁₋₄-alkyl or an oxo group, or R' and R₂ together represent a bond,
- R'' is H or C₁₋₄-alkyl, and the dotted lines can represent a single or double bond,

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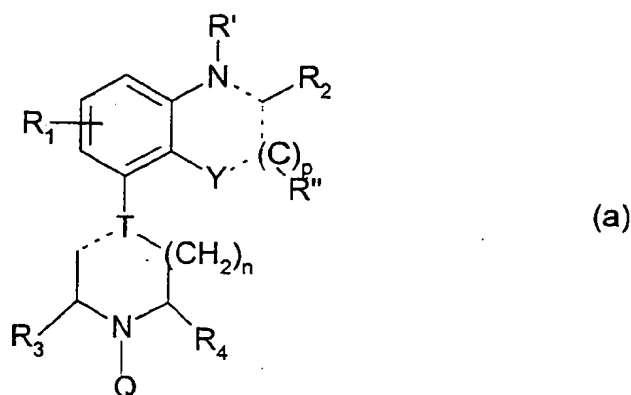
- p has the value 0-2,
- Y represents C, O, N or S,
- T represent N or C,
- R₃ and R₄ independently are hydrogen or C₁₋₄-alkyl,
- n has the value 1 or 2,
- Q is a group of the formula -CH₂-C(R₅R₆)-Z-R₇ wherein R₅ and R₆ represent H or C₁₋₇-alkyl, C₁₋₃-alkylphenyl, Z represents -C(R₈R₉)-O-, -C(R₈R₉)-C(=O)-, -C(R₈R₉)-C(=NOR₁₀)-, -NH-C(=O)- or -O-CH₂-, wherein R₈ - R₁₀ represent H or C₁₋₄-alkyl, and R₇ is a 5- or 6-membered cyclic group, aromatic group or hetero-aromatic group, or the 1- or 2-adamantyl group, which group R₇ can be substituted with O-C₁₋₄-alkyl, CN, halogen or C₁₋₄-alkyl,

with the proviso that R₇ cannot be 1-alkylcycloalkyl, and that compounds wherein Z is the group-NH-C(=O)- and R₅=R₆=H, T is nitrogen, and the bicyclic group is 1,4-benzoxazin-8-yl, quinoxalin-5-yl, quinolin-5-yl, indol-4-yl, benzoxazol-7-yl, benzimidazol-4-yl, benzothiazol-7-yl are not included, and salts thereof.

These compounds have high affinity for both the dopamine D₂ receptors and serotonin 5-HT_{1A} receptors.

Description

[0001] The invention relates to a group of new piperazine compounds having interesting pharmacological properties. It has been found that compounds of the formula (a)



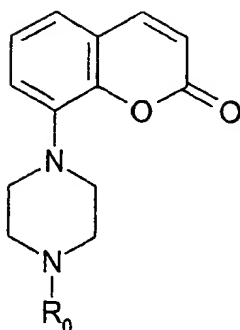
wherein

- R_1 is hydrogen or fluoro,
- R' is H or C_{1-4} -alkyl,
- R_2 is H, C_{1-4} -alkyl or an oxo group, or R' and R_2 together represent a bond,
- R'' is H or C_{1-4} -alkyl, and the dotted lines can represent a single or double bond,
- p has the value 0-2,
- Y represents C, O, N or S,
- T represent N or C,
- R_3 and R_4 independently are hydrogen or C_{1-4} -alkyl,
- n has the value 1 or 2,
- Q is a group of the formula $-CH_2-C(R_5R_6)-Z-R_7$ wherein R_5 and R_6 represent H or C_{1-7} -alkyl, C_{1-3} -alkylphenyl, Z represents $-C(R_8R_9)-O-$, $-C(R_8R_9)-C(=O)-$, $-C(R_8R_9)-C(=NOR_{10})-$, $-NH-C(=O)-$ or $-O-CH_2-$, wherein $R_8 - R_{10}$ represent H or C_{1-4} -alkyl, and R_7 is a 5- or 6-membered cyclic group, aromatic group or hetero-aromatic group, or the 1- or 2-adamantyl group, which group R_7 can be substituted with $O-C_{1-4}$ -alkyl, CN, halogen or C_{1-4} -alkyl, with the proviso that R_7 cannot be 1-alkylcycloalkyl, and that compounds wherein Z is the group $-NH-C(=O)-$ and $R_5=R_6=H$, T is nitrogen, and the bicyclic group is 1,4-benzoxazin-8-yl, quinoxalin-5-yl, quinolin-5-yl, indol-4-yl, benzoxazol-7-yl, benzimidazol-4-yl, benzothiazol-7-yl are not included, and salts thereof have interesting pharmacological properties.

[0002] Preferred compounds according to the invention are compounds having formula (a) wherein T represents nitrogen, R' is hydrogen, and the other symbols have the above meanings.

[0003] Especially preferred are compounds of formula (a) wherein Y is carbon and T is nitrogen, $p=1$, $n=1$, R_1 , R' , R_2 , R'' , R_3 and R_4 are hydrogen, the dotted lines are single bonds, and Q is a group of the formula $-CH_2-C(R_5R_6)-Z-R_7$ wherein R_5 and R_6 represent H, C_{1-4} -alkyl or benzyl, Z is $-C(R_8R_9)-C(=O)-$, $-C(R_8R_9)-O-$ or $-NH-C(=O)-$, wherein R_8 and R_9 represent hydrogen or methyl, and R_7 is phenyl optionally substituted with halogen, CN, CH_3 or OCH_3 . If Z is $-NH-C(=O)-$ or $-CH_2-O-$, $R_5=H$ and R_6 is alkyl or alkylphenyl, then the R-configuration at the chiral C-atom carrying R_5 and R_6 is preferred.

[0004] It is known from EP 0650964 that compounds of the formula



wherein R_0 is C_{1-4} -alkyl, which compounds can be substituted in the phenyl group and/or heterocyclic group and/or the piperazine group, act on the central nervous system by binding to 5-HT receptors. In particular these compounds bind to subtypes of the 5-HT-receptor, i.e. 5-HT_{1A} and 5-HT_{1D} receptors.

[0005] It has now surprisingly been found that the compounds according to the invention show high affinity for both the dopamine D₂ and serotonin 5-HT_{1A} receptors (pK_i range 7.0-9.5 for both receptor types). This combination is useful for the treatment of schizophrenia and other psychotic disorders and might allow for a more complete treatment of all disease symptoms (e.g. positive symptoms, negative symptoms and cognitive deficits).

[0006] The compounds show varying activities as either partial agonists or antagonists at dopamine D₂-, D₃- and D₄-receptors. Some compounds show agonist-like effects at dopamine receptors, however they potently antagonize apomorphine-induced climbing behaviour in mice (ED₅₀ values <1 mg/kg p.o). The compounds show varying activity as 5-HT_{1A} receptor agonists and induce aspects of the serotonin behavioural syndrome to differing intensities.

[0007] The compounds are active in therapeutic models sensitive to clinically relevant antipsychotics (e.g. the conditioned avoidance response; Van der Heyden & Bradford, Behav. Brain Res., 1988, 31:61-67), antidepressants (e.g. differential reinforcement of low rate responses; van Hest et al., Psychopharmacology, 1992, 107:474-479) and anxiolytics (e.g. suppression of stress-induced vocalization; van der Poel et al., Psychopharmacology, 1989, 97: 147-148).

[0008] In contrast to clinically relevant dopamine D₂ receptor antagonists the described compounds have a low propensity to induce catalepsy in rodents and as such are likely to induce less extrapyramidal side effects than existing antipsychotic agents.

[0009] The 5-HT_{1A} receptor agonism inherent in these compounds may be responsible for the reduced tendency to induce extrapyramidal effects and the therapeutic effects observed in behavioural models sensitive to either antidepressants or anxiolytics.

[0010] The compounds are likely to be of value for the treatment of affections or diseases of the central nervous system caused by disturbances in either the dopaminergic or serotonergic systems, for example: aggression, anxiety disorders, autism, vertigo, depression, disturbances of cognition or memory and in particular schizophrenia and other psychotic disorders.

[0011] Suitable acids with which the compounds can form pharmaceutically acceptable acid addition salts are for example hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, and organic acids such as citric acid, fumaric acid, maleic acid, tartaric acid, acetic acid, succinic acid, benzoic acid, p-toluene sulphonic acid, methanesulphonic acid and naphthalene-sulphonic acid.

[0012] The compounds of the invention can be brought into forms for administration by means of usual processes using auxiliary substances such as liquid and solid carrier materials.

[0013] The compounds of the invention can be obtained according to a number of synthetic routes (A to D) as described hereafter. The piperazines and homopiperazines used in these methods are indicated as I-H to XVIII-H, wherein I to XVIII represent the following groups (fig. 1):

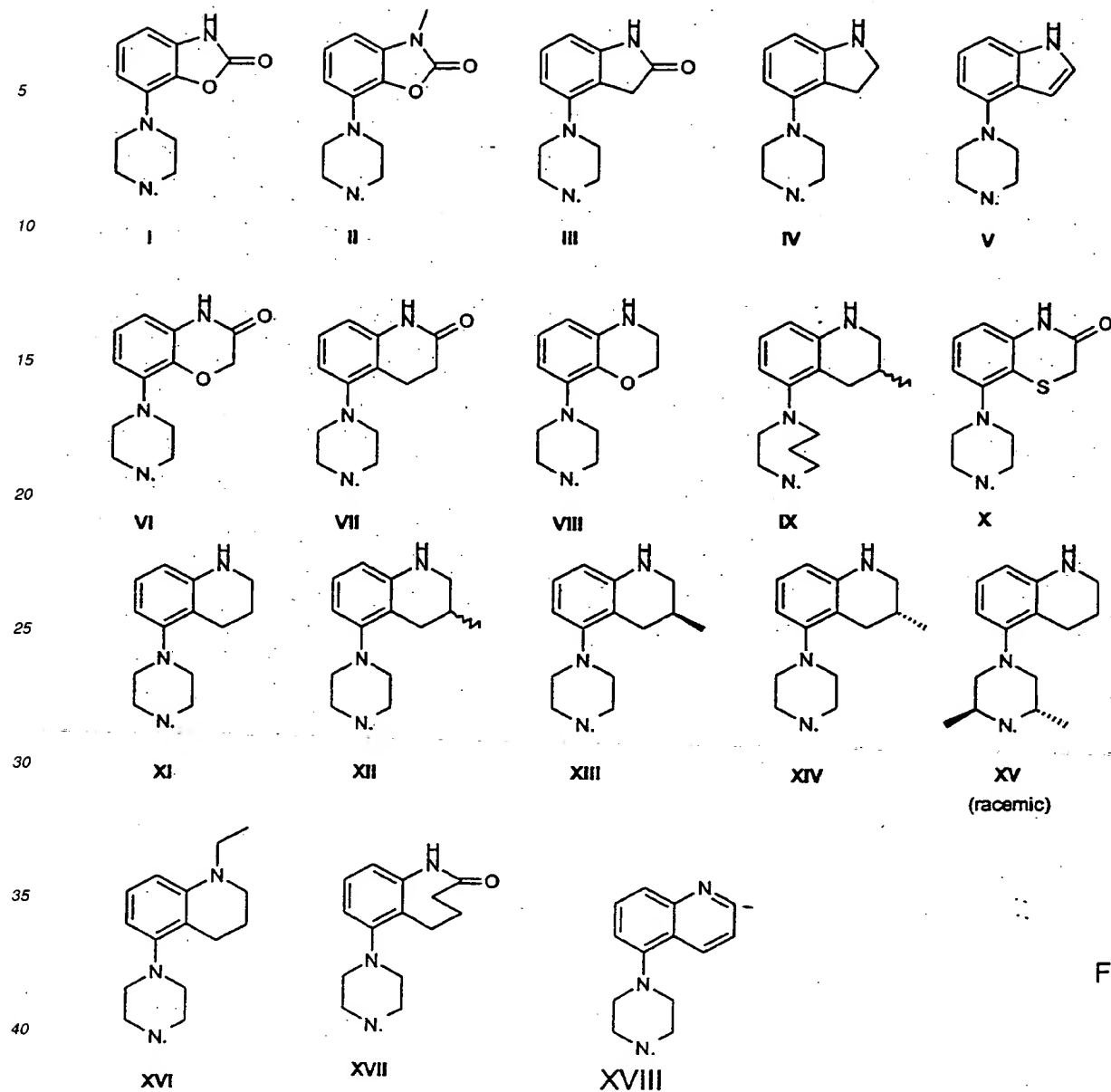
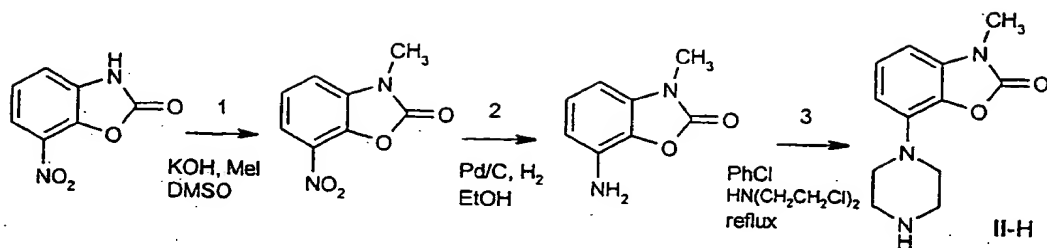
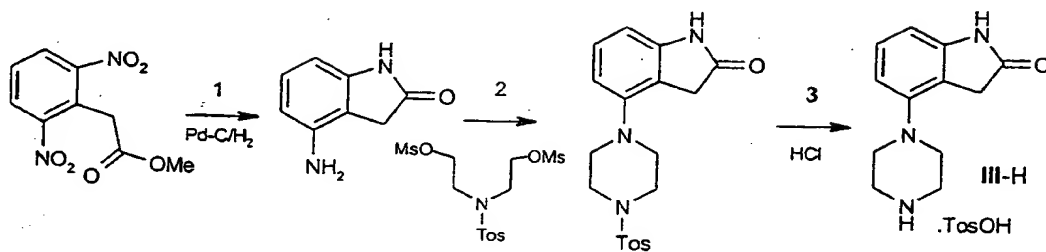


Fig. 1

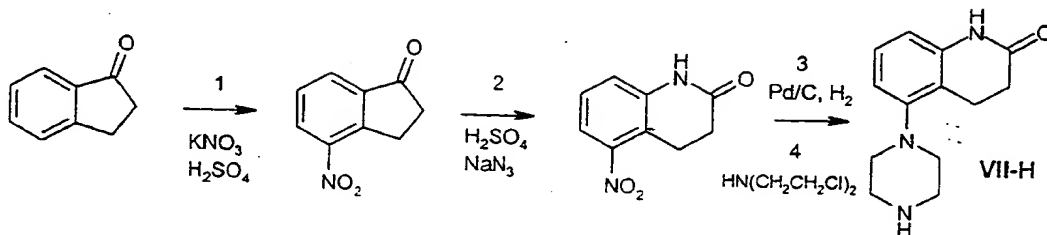
[0014] The syntheses of the piperazines I-H, IV-H, V-H, VI-H, VIII-H, XI-H, XII-H and XVIII-H have been described in EP 0189612 and/or EP 0138280, or can be prepared in an analogous manner. The syntheses of the remaining piperazines is given below (schemes i to vii).

Synthesis of II-H:

scheme i

Synthesis of III-H:

scheme ii

Synthesis of VII-H:

scheme iii

Step 1 (scheme iii):

- 55 [0015] This step can be carried out according to the procedure described in: C.K. Ingold, H.A. Piggott, *J. Chem. Soc.(II)*, (1923), 1469.

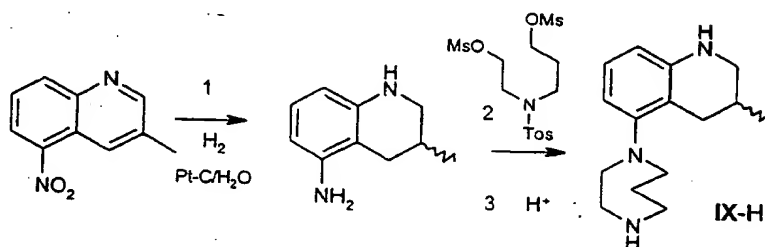
Step 2 (scheme iii):

[0016] This step can be carried out according to the procedure described in: M. Tomita, S. Minami, *J. Chem. Soc. (C)*, (1969), 183.

Steps 3 and 4 (scheme iii):

[0017] Steps 3 and 4 can be carried out according to procedures described in EP 0189612.

Synthesis of IX-H:

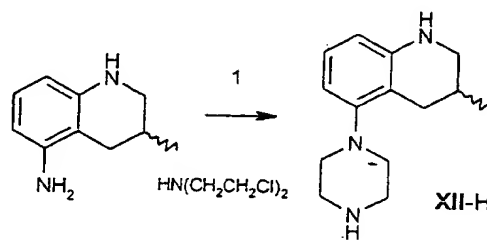


scheme iv

Moiety of X-H:

[0018] X-H was not used as an intermediate in the synthesis. The fragment was built in a different manner, see "Remark about D3" in the last part of the examples (*vide infra*).

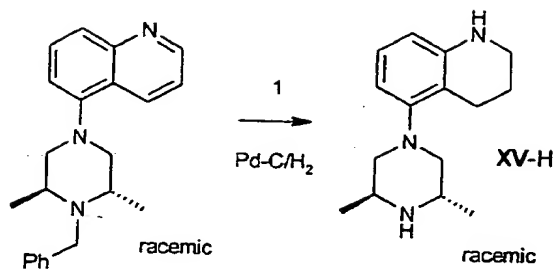
Synthesis of XII-H:



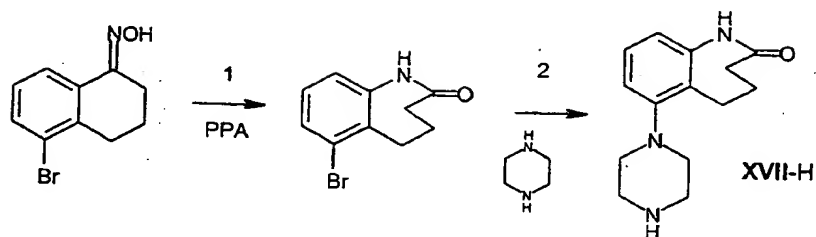
scheme v

Step 1 (scheme v):

[0019] Transforming the aniline (see also scheme iv) into the corresponding piperazine XII-H can be carried out according to the procedure described in EP 0189612.

Synthesis of XV-H:

scheme vi

Synthesis of XVII-H:

scheme vii

[0020] The H-atom of the N-H moiety of compounds I-H to XVII-H can be replaced by group Q in four different chemical ways (A, B, C, and D vide infra), eventually leading to the compounds of the invention.

Groups Q

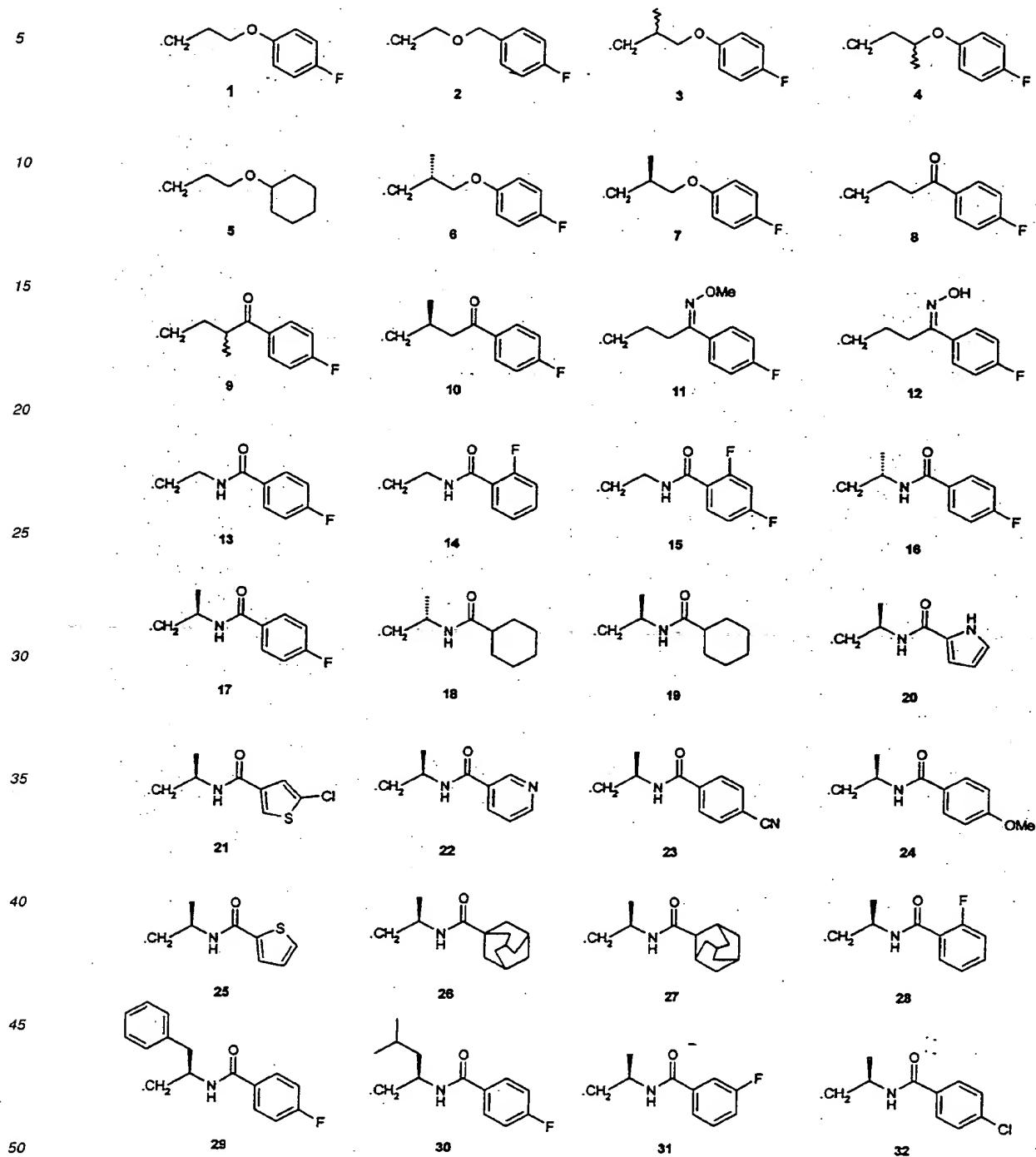
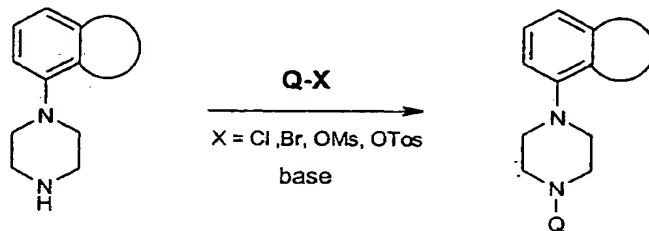


Fig. 2

[0021] A number of Q-Cl or Q-Br compounds are commercially available, others can be obtained according to standard chemical procedures as illustrated in the examples showing the preparation of these intermediates.

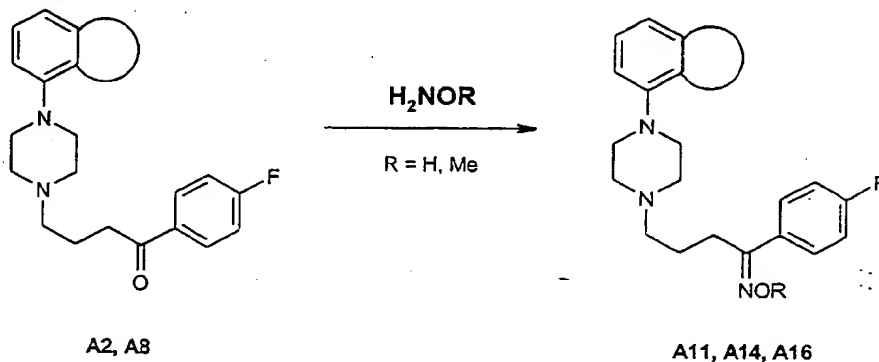
Synthesis routes A to D:

[0022] The compounds listed in table A, except for A11, A14 and A16, were prepared via the synthesis depicted in scheme A1 (*vide infra*): a piperazine (see fig. 1) was reacted with Q-X (X = Cl, Br, OMs, OTos) in *e.g.* acetonitrile with Et(*i*-Pr)₂N acting as a base; in some cases KI (or NaI) was added. Et₃N can be used instead of Et(*i*-Pr)₂N.



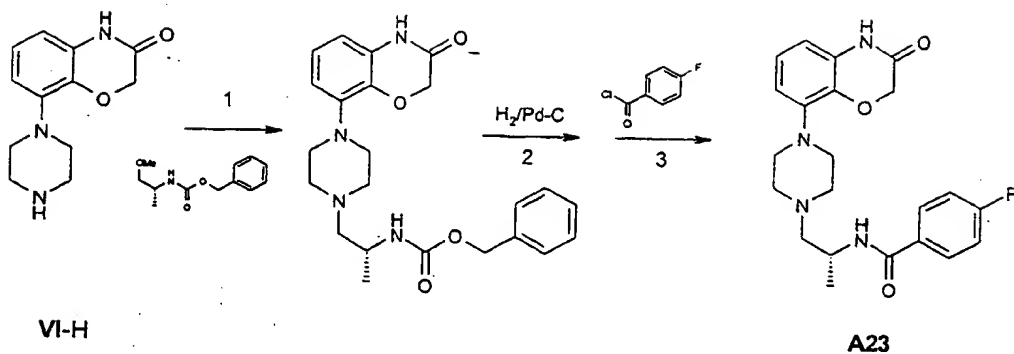
scheme A1

[0023] Compounds A11, A14 and A16 were prepared according to the synthesis given in scheme A2: reaction of A2 and A8 with hydroxylamine (derivatives) yielded the desired compounds.



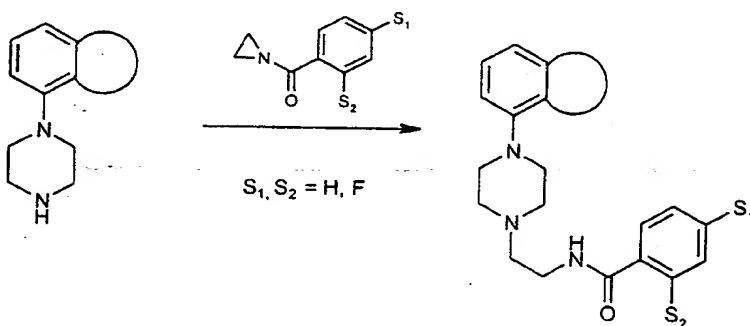
scheme A2

[0024] Compound A23 can be obtained according to a variation of the synthesis depicted in scheme A1, as indicated in scheme A3.



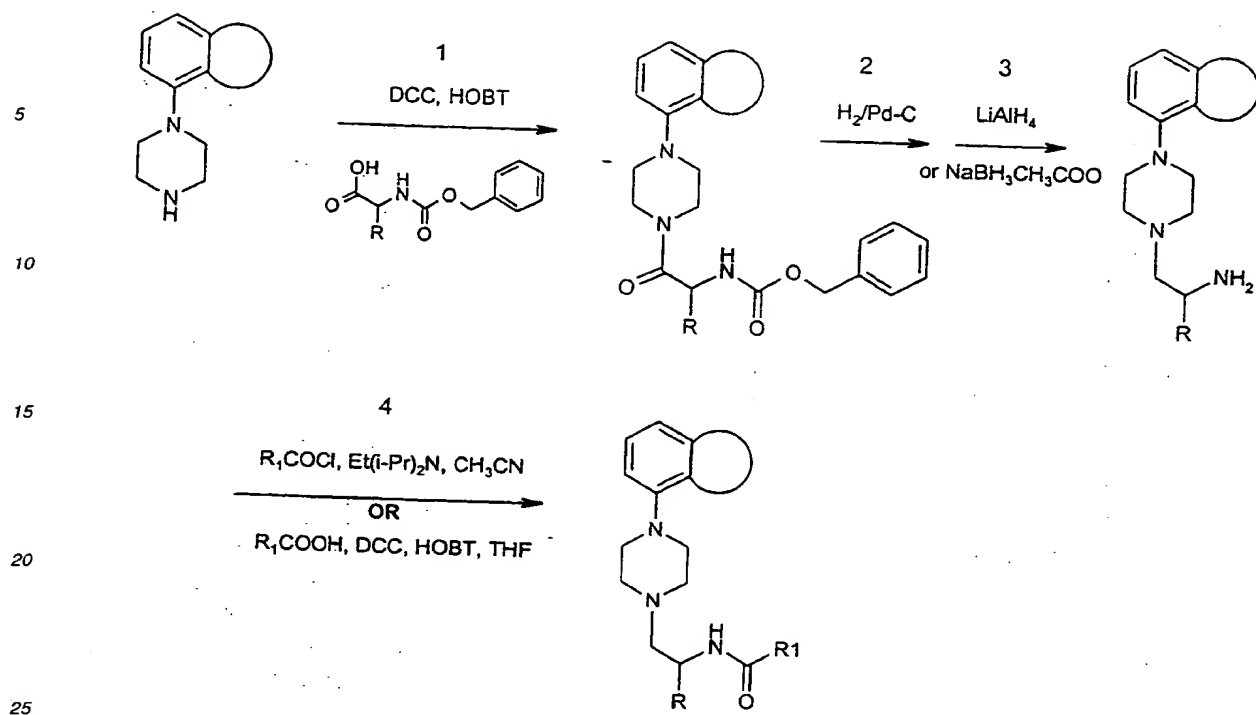
scheme A3

[0025] The compounds listed in table B, were synthesized according to the reaction depicted in scheme B. Piperazines were reacted with N-benzoyl-aziridines to yield the compounds of the invention.



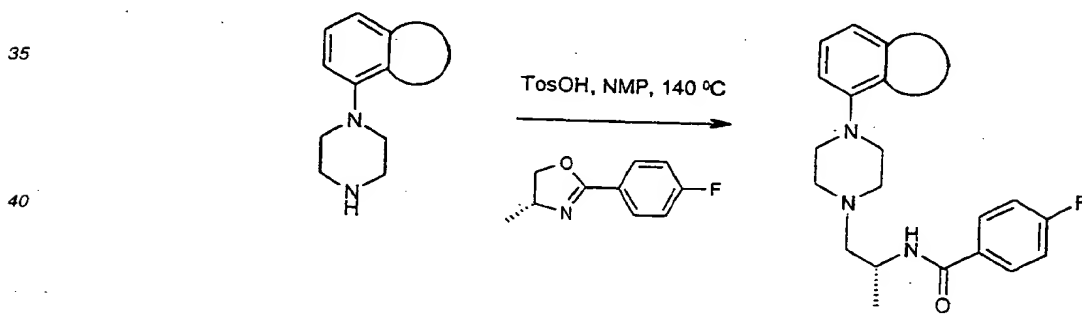
scheme B

[0026] In scheme C a piperazine is coupled to a protected amino acid (step 1) to yield an intermediate which gives after two reductions (steps 2,3) a (optically active) primary amine. This amine can be derivatized easily by treatment with e.g. acid chlorides (step 4), yielding the products of the invention.



Scheme C

30 [0027] According to route D the synthesis of the desired compounds is achieved by reacting a piperazine with the optically active (R)-2-*para*-fluorophenyl-4-methyl-4,5-dihydro-oxazole, see scheme D.



scheme D

50 [0028] The preparation of the compounds of formula (a) and of a number of intermediate compounds will now be described in detail in the following Examples.

Abbreviations:

55 [0029]

BINAP bis(diphenylphosphino)-1,1'-binaphthyl

dba	dibenzylideneacetone. (1,5-diphenyl-1,4-pentadien-3-one)
DCC	dicyclohexylcarbodiimide
DMSO	dimethylsulfoxide
Et ₃ N	triethylamine
5 Et(<i>i</i> -Pr) ₂ N	diisopropylethylamine
EtOAc	ethyl acetate
HOBT	1-hydroxybenztriazole
Ms	mesyl
Tos	tosyl

Examples:**Example 1: preparation of A8.2HCl (see scheme A1)**

15 **[0030]** While stirring, 0.7 g (3.2 mmol) of piperazine XI-H was dissolved in 20 ml of acetonitrile, after which 0.5 g (3.9 mmol) of di-isopropyl-ethyl-amine and 0.65 g (3.2 mmol) of Q8-Cl were added. The reaction mixture was refluxed for 18 hrs after which the reaction was allowed to reach room temperature. The reaction mixture was concentrated *in vacuo*, after which the residue was subjected to column chromatography (SiO₂, eluent: CH₂Cl₂/MeOH = 98/2) yielding 0.4 g of an oil. The latter oil was treated with 2.5 equivalents of 0.5 M HCl/MeOH, yielding 0.4 g of almost pure A8.2HCl. m.p.:
 20 dec. > 260 °C. ¹H-NMR(CDCl₃/DMSO = 1/4) δ: 1.95(m, 2H), 2.13(m, 2H), 2.77(m, 2H), 3.10-3.30(cluster, 10H), 3.33(m, 2H), 3.40-3.90(cluster, 2H), 6.86-7.04(cluster, 2H), 7.24(t, 1H), 7.34(m, 2H), 8.08(m, 2H), 10.8(broad, 1H).

Example 2: preparation of A11.2HCl (see scheme A2)

25 **[0031]** 0.54 g (1.4 mmol) of A8 (free base) was dissolved in 15 ml of MeOH together with 0.11 ml of pyridin and 0.14 g (1.67 mmol) of MeONH₂·HCl. The reaction mixture was stirred and heated at 50 °C for 2.5 hrs, after this period an extra equivalent of MeONH₂·HCl and 1 ml of di-isopropyl-ethyl-amine were added, the reaction was continued for 6 hrs. The reaction mixture was allowed to reach room temperature, after which it was concentrated *in vacuo*. The residue was taken in saturated NaHCO₃ solution, the latter was extracted with EtOAc. The organic fraction was dried on
 30 MgSO₄, after removal of the drying agent and the solvent *in vacuo*, the resulting oil was subjected to column chromatography (SiO₂, eluent: EtOAc) yielding 0.40 g of a brownish oil which subsequently was treated with 2.5 equivalents of 0.5 M HCl/MeOH to yield 0.37 g (0.77 mmol, 55%) of A11.2HCl as a white solid. m.p.: 218-222 °C. ¹H-NMR(CDCl₃/DMSO = 1/4) δ: 1.92-2.04(m, 4H), 2.72-2.84(m, 4H), 3.10-3.28(cluster, 8H), 3.34(m, 2H), 3.53(m, 2H), 3.95(s, 3H), 6.98(m, 2H), 7.20(m, 2H), 7.25(t, 1H), 7.76(m, 2H), 11.05(broad, 1H), 10.2-11.8(broad, 1H). The E/Z ratio
 35 was 95/5.

Example 3: preparation of A3 (see scheme A3)

[0032] Step 1 (scheme A3): 1.62 g (7 mmol) of piperazine VI-H, 2.0 g (7 mmol) of O-mesyl-N-benzyloxycarbonyl-(R)-alaninol, 0.84 g (8.4 mmol) of Et₃N and a small amount of KI were dissolved in 30 ml of acetonitril. While stirring, the reaction mixture was refluxed for 0.5 hr during which a white precipitate had formed. The precipitate was removed by filtration. To the filtrate SiO₂ was added and the resulting slurry was subjected to evaporation to remove the acetonitril. The resulting dry SiO₂ powder with the reaction mixture absorbed on it, was placed on top of a dry SiO₂ column (flexible), after which elution was performed with EtOAc. The product containing part of the column was cut out and the product was washed from the SiO₂ with MeOH. The resulting MeOH solution was concentrated and subsequently EtOAc was added, the latter solution being dried on MgSO₄. After removal of the drying agent and the solvent *in vacuo*, the pure intermediate product was isolated in 25% yield (0.75 g).

[0033] Step 2 (scheme A3): 0.75 g (1.8 mmol) of the latter compound was dissolved in a mixture of 4 ml of EtOAc and 8 ml of MeOH. Then, under a nitrogen atmosphere, a little of 10% Pd-C was added to the mixture after which hydrogenation was performed. After 2 hrs. the reaction mixture was filtered and the filtrate concentrated *in vacuo* leaving a residue of 0.48 g (93%) of crude primary amine. This was used without further purification in step 3.

[0034] Step 3 (scheme A3): 0.48 g (1.65 mmol) of primary amine was dissolved in 20 ml of CHCl₃. While stirring, 0.33 g (3.3 mmol) of Et₃N and 0.26 g (1.65 mmol) of *para*-fluorobenzoylchloride were added. After 16 hrs SiO₂ was added to the reaction mixture and the resulting slurry was subjected to evaporation to remove the CHCl₃. The resulting dry SiO₂ powder with the reaction mixture absorbed on it, was placed on top of a dry SiO₂ column (flexible), after which elution was performed with EtOAc. The product containing part of the column was cut out and the product was washed from the SiO₂ with MeOH. The resulting MeOH solution was concentrated and subsequently EtOAc was added, the latter solution being dried on MgSO₄. After removal of the drying agent and the solvent *in vacuo*, 0.25 g (36%) of the free

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base of **A23** was obtained. m.p.: 245-7 °C. ¹H-NMR(CDCl₃/DMSO = 1/4) δ: 1.18(d, 3H, J=6Hz), 2.35(dd, 1H, J=7 and J=12 Hz), 2.54-2.62(m, 5H), 2.98(m, 4H), 4.23(m, 1H), 4.5(s, 2H), 6.50-6.56(cluster, 2H), 6.82(t, 1H, J≈8 Hz), 7.23(m, 2H), 7.92(m, 2H), 8.12(d, 1H, J≈8 Hz), 10.5(s, 1H).

5 Remark

[0035] **A20** was prepared from piperazine I-X and the crude diethylketal of **Q10-Br** (for the preparation of the latter, see preparation of **Q10-Br**) according to scheme A1. This yields on its turn the diethyl ketal of the product **A20**, which was transformed into **A20.HCl** by treating the diethyl ketal with aqueous 2 M Hcl.

Table A

compound	piperazine	Q	X	salt	melting point °C
A1	I	1	Cl	HCl	225-7
A2	I	8	Cl	HCl	260-3
A3	I	5	OMs	HCl	180-2
A4	XII	1	Cl	2HCl	201-4
A5	XI	1	Cl	2HCl	218-20
A6	I	3	Cl	HCl	209-12
A7	I	4	OTos	HCl	205-8
A8	XI	8	Cl	2HCl	>260 d
A9	XI	3	Cl	2HCl	190-2
A10	XI	4	OTos	2HCl	225-9
A11	XI	11	prep. from A8	2HCl	218-21
A12	I	2	OMs	---	154-5
A13	XI	2	OMs	1.3HCl	186-7
A14	I	11	prep. from A2	HCl	224-7
A15	I	9	Br	HCl	150-5
A16	XI	12	prep. from A8	---	171-3
A17	II	1	Cl	---	137-8
A18	I	7	OMs	HCl	207.5-10
A19	XI	9	Br	2HCl	>140 d
A20	I	10	Br	HCl	>130 d
A21	XI	7	OMs	FUM	foam
A22	I	6	OMs	HCl	204-6
A23	VI	17	OMs	---	245-7
A24	IX	1	Cl	2HCl	205

Example 4: preparation of **B4** (see scheme B)

[0036] A solution of 0.75 g (3.45 mmol) of piperazine XI-I in 10 ml of dry tetrahydrofuran (THF) was added to a solution of 0.63 g (3.79 mmol) of N-(*para*-fluoro-benzoyl)aziridine in 8 ml of dry THF. The reaction mixture was stirred at reflux temperature for 2 hrs after which it was allowed to reach room temperature. The solvent was removed *in vacuo*, the residue subjected to flash column chromatography (SiO₂, eluent: CH₂Cl₂/MeOH = 98/2) yielding 0.51 g (39%) of glassy product **B4**. m.p.: 150-2 °C. ¹H-NMR(CDCl₃/DMSO = 1/4) δ: 1.88 (m, 2H), 2.55-2.65(cluster, 8H), 2.94(m, 4H), 3.30(m, 2H), 3.57(m, 2H), 3.87(broad, 1H), 6.26(d, 1H, J=8Hz), 6.38(d, 1H, J=8Hz), 6.87(t broad, 1H), 6.95(t, 1H,

J=8Hz), 7.13(m, 2H), 7.81(m, 2H).

Table B

compound	piperazine	Q	salt	melting point °C
B1	XII	13	2HCl	192-5
B2	XV	13	2HCl	230-3
B3	I	13	---	> 300 dec
B4	XI	13	---	150-2
B5	I	14	---	235-8
B6	I	15	---	265-70
B7	XIII	13	---	178-9
B8	XIV	13	---	179-80

Example 5: preparation of C10.2HCl (see scheme C)

[0037] Step 1 (scheme C): 3.2 g (15 mmol) of piperazine VIII-H was dissolved in 45 ml of dry THF. While stirring and under a nitrogen atmosphere, 3.35 g (15 mmol) of (R)-N-(benzyloxycarbonyl)-alanine and 2.03 g (15 mmol) of 1-hydroxybenzotriazole were added to the solution. The resulting mixture was brought to 0 °C, after which 3.0 g (15 mmol) of dicyclohexylcarbodiimide were added. After 1.5 hrs the precipitate was removed by filtration. To the filtrate SiO₂ was added after which the solvent was removed. The resulting dry SiO₂ powder with the reaction mixture absorbed on it, was placed on top of a dry SiO₂ column (flexible), after which elution was performed with EtOAc/MeOH/NH₄OH = 97/2.7/0.3. The product-containing part of the column was cut out and the product was washed from the SiO₂ with MeOH. The resulting MeOH solution was concentrated and subsequently EtOAc (and a little absolute MeOH) was added, the latter solution being dried on MgSO₄. After removal of the drying agent and the solvent *in vacuo*, 6.1 g (96%) of the desired intermediate was isolated.

[0038] Step 2 (scheme C): 6.1 g (14 mmol) of the latter intermediate were dissolved in a mixture of 30 ml EtOAc and 70 ml of MeOH after which a catalytic amount of 10% Pd-C was added. Subsequently the mixture was hydrogenated at atmospheric pressure. After 16 hrs an extra amount of 10% Pd-C was added. Another 16 hrs later, the reaction mixture was filtered and concentrated *in vacuo*, leaving a residue which was subjected to flash column chromatography (SiO₂, eluent: CH₂Cl₂/MeOH/NH₄OH = 92/7.5/0.5), yielding 2.05 g (50%) of the primary amine.

[0039] Step 3 (scheme C): 2.05 g (7.1 mmol) of the latter primary amine were suspended in 9 ml of 1,2-dimethoxyethane, after which 1.32 g (35 mmol, 5 eq.) of NaBH₄ were added. Then the mixture was brought to 0 °C, after which a solution of 2.1 g (35 mmol) acetic acid in 7 ml 1,2-dimethoxyethane was carefully added to the mixture. When the addition was completed, the reaction mixture was brought to 85 °C. After a period of 1 hour the reaction was allowed to reach room temperature, the reaction mixture was acidified to pH 2 (aqueous 2 M HCl) and heated again until the temperature reached 60 °C, which situation was continued for 0.5 hrs. After this period, the reaction mixture was allowed to reach room temperature again and its pH was adjusted to 7-8 by adding aqueous 2 M NaCl. Extraction was performed with EtOAc, the organic fraction was washed with saturated NaCl/water and dried on Na₂SO₄. After removal of the drying agent and the solvent *in vacuo*, 0.73 g (37%) of a yellow oil containing the reduced amine intermediate was obtained. This was used without further purification for step 4 (*vide infra*).

[0040] Step 4 (scheme C): 0.73 g (2.6 mmol) of the reduced amine intermediate and 0.53 g (5.3 mmol) of Et₃N were dissolved in 35 ml CH₃CN. While stirring, a solution of 0.37 g (2.36 mmol) *para*-fluorobenzoylchloride in 7 ml of CH₃CN was added slowly and dropwise. After 16 hrs the reaction mixture was concentrated *in vacuo*, leaving a residue which was subjected to flash column chromatography (SiO₂, eluent: CH₂Cl₂/MeOH = 97/3), yielding an oil (free base) which was treated with 2.0 equivalents of 0.5 M HCl/MeOH to give 0.3 g (24%) of hygroscopic C10.2HCl-salt. [α]_D²⁵ -59° (MeOH, 12.0 mg/ml). ¹H-NMR(CDCl₃/DMSO = 1/4) δ : 1.28(d, 3H, J=6 Hz), 3.0-3.7(cluster, 12H), 3.7-4.2(broad, 2H), 4.25(t, 2H, J=3 Hz), 4.57(m, 1H), 6.44-6.60(cluster, 2H), 6.72(t, 1H, J=8 Hz), 7.25(m, 2H), 8.08(m, 2H), 8.8(d, 1H, J=8 Hz), 10.3 (s broad, 1H).

Remark

[0041] The two diastereomeric compounds C8 and C9 were prepared by reacting the racemic piperazine XII-H with optically pure (R)-N-(benzyloxycarbonyl)-alanine following the synthetic pathway depicted in scheme C. After step 4

(scheme C) a diastereomeric mixture was obtained which was separated into its pure components by HPLC.

Table C

compound	piperazine	Q	salt	melting point °C
C1	XI	19	2HCl	182-4
C2	XI	16	2HCl	238-43
C3	XI	17	2HCl	240-3
C4	XI	18	2HCl	216-9
C5	XI	20	2HCl	>180 d
C6	XI	22	2HCl	175
C7	XI	21	2HCl	>168 d
C8	XIII or XIV	17	0.5FUM	amorf
C9	XIV or XIII	17	0.67FUM	amorf
C10	VIII	17	2HCl	$[\alpha]_D^{25} -59^\circ$
C11	XI	32	2HCl	178-83 d
C12	XI	23	2HCl	193-9 d
C13	XI	24	2HCl	175-80 d
C14	XI	28	2HCl	173-8 d
C15	XI	31	2HCl	>165 d
C16	XI	25	HCl	115-20 d
C17	XI	26	HCl	220-5 d
C18	XI	27	HCl	130-5 d
C19	XI	29	2HCl	220-2
C20	XI	30	2HCl	225

Example 6: preparation of D1 (see scheme D)

[0042] 0.94 g (4.3 mmol) of piperazine I-H together with 0.77 g (4.3 mmol) of (R)-2-*para* fluorophenyl-4-methyl-4,5-dihydro-oxazole (*vide infra*) and 0.16 g (0.84 mmol) of *para*-toluenesulfonic acid were dissolved in 4 ml of N-methyl-pyrrolidone. The mixture was stirred under a nitrogen atmosphere at 135 °C. After 12 hrs the reaction mixture was allowed to reach room temperature after which 40 ml of EtOAc, 20 ml of water and 4 ml of aqueous 2 M NaOH were added. The latter mixture was shaken vigorously, after standing the organic fraction was separated and washed with water and dried on Na₂SO₄. The drying agent was removed by filtration, to the filtrate SiO₂ was added after which the solvent was removed. The resulting dry SiO₂ powder with the organic fraction absorbed on it, was placed on top of a dry SiO₂ column (flexible), after which elution was performed with CH₂Cl₂/MeOH = 87/13. The product-containing part of the column was cut out and the product was washed from the SiO₂ with MeOH. The resulting MeOH solution was concentrated and subsequently CH₂Cl₂/MeOH = 80/20 was added, the latter solution being dried on Na₂SO₄. After removal of the drying agent and the solvent *in vacuo*, a solid was isolated which was suspended in EtOAc/EtOH = 5/1 and stirred for 0.5 hrs at reflux temperature. After the suspension had reached room temperature, filtration took place yielding a residue: 0.29 g (16%) of pure D1. m.p.: 240-2 °C. ¹H-NMR(CDCl₃/DMSO = 1/4) δ: 1.19(d, 3H, J=6 Hz), 2.32-2.70(cluster, 6H), 3.12-3.22(m, 4H), 4.25(m, 1H), 6.56(m, 1H), 6.60(m, 1H), 6.98(t, 1H, J=8 Hz), 7.23(m, 2H), 7.92(m, 2H), 8.15(d, 1H, J=8 Hz), 11.5(broad, 1H).

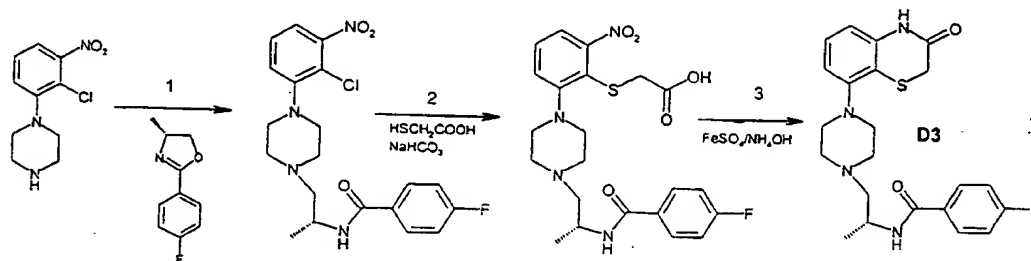
55 Preparation of (R)-2-*para* fluorophenyl-4-methyl-4,5-dihydro-oxazole

[0043] 25 g (0.21 mol) of *para*-fluorobenzonitril together with 16.5 g (0.22 mol) of (R)-2-amino-1-propanol and 4.56 g (0.033 mol) of K₂CO₃ were mixed together in a solution of 70 ml of ethyleneglycol and 40 ml of glycerol. This mixture

was heated at 105 °C for 24 hrs under a nitrogen atmosphere, after which the reaction mixture was allowed to reach room temperature. Subsequently 150 ml of *n*-hexane and 300 ml of water were added, the resulting mixture was agitated after which the organic fraction was separated and dried on Na₂SO₄. After removal of the drying agent and the solvent *in vacuo*, 15 g (40%) of the crude oxazol was isolated as a yellow oil. This was used without further purification in the syntheses of the D-compounds.

Remark

[0044] D3 was made in the following way:



[0045] Step 1 was carried out analogously to the preparation of D1 (see example 6), steps 2 and 3 were carried out analogously to the syntheses described by Cechetti, *Eur. J. Med. Chem.*, **24**, (1989), 479.

Table D

compound	piperazine	Q	salt	melting point °C
D1	I	17	---	240-2 d
D2	VII	17	---	250-2
D3	X	17	---	237-8
D4	III	17	---	187-9
D5	IV	17	2. HCl	150 d
D6	V	17	HCl	225-7 d
D7	XVII	17	HCl	148-52 d
D8	XVIII	17	HCl	[α] _D ²⁵ -46°

INTERMEDIATES used in route A.

Step 1 (scheme i):

[0046] 3.94 g (21.9 mmol) of 7-nitro-2-benzoxazolidinone (for preparation of the latter compound, see EP 0189612 and references cited therein), were dissolved in 40 ml of DMSO after which 1.72 g of 85% powdered KOH (26.2 mmol) were added. While stirring and cooling (water) 3.72 g (26.2 mmol) of MeI dissolved in 6 ml of DMSO, were added dropwise over a period of 10 minutes. Stirring was continued at room temperature for 16 hrs, during the latter period an extra amount of MeI (0.5 g) was added. After the reaction was completed, the reaction mixture was diluted with water after which extraction took place with CH₂Cl₂. The combined organic fractions were washed with water and brine respectively, after which the organic fraction was dried on MgSO₄. After removal of the drying agent and evaporation of the solvent *in vacuo*, 4.1 g of a solid residue was left. Flash column chromatography (SiO₂, eluent: CH₂Cl₂) of the latter yielded 3.6 g (85%) of pure 3-methyl-7-nitro-2-benzoxazolidinone.

[0047] Steps 2 and 3 were carried out as described in EP 0189612

Step 1 (scheme ii):

[0048] 10.6 g (42 mmol) of (2,6-dinitro-phenyl)-acetic acid methyl ester was dissolved in a mixture of 200 ml of EtOAc and 50 ml of MeOH. A catalytic amount of 10% Pd-C was added and the solution was shaken under atmospheric H₂ pressure at room temperature. After the calculated amount of H₂ was taken up by the reaction mixture, the catalyst was removed by filtration and the filtrate concentrated *in vacuo*. It was attempted to crystallize the wanted intermediate from warm EtOAc, only darkening of the solution occurred. Removal of the solvent and subsequent flash chromatography of the residue (SiO₂, eluent: CH₂Cl₂/MeOH = 97/3) yielded 4.6 g (74%) of the wanted aniline as a brown solid.

Step 2 (scheme ii):

[0049] 1.4 g (9.4 mmol) of the aniline and 4.1 g (9.9 mmol) of TosN(CH₂CH₂OMs)₂ were dissolved in 40 ml of chlorobenzene. While stirring, 4.35 ml (25 mmol) of diisopropylethylamine were added after which the temperature was raised to 140 °C for 8 hrs. After the reaction mixture had reached room temperature, it was concentrated *in vacuo* and subsequently the residue was subjected to flash chromatography (SiO₂, eluent: CH₂Cl₂/MeOH = 97/3) which yielded 0.9 g (26%) of a greenish solid containing the tosylated piperazine.

Step 3 (scheme ii):

[0050] 0.9 g (2.4 mmol) was dissolved in 2 ml of concentrated HCl and heated at reflux temperature for 16 hrs after which the reaction mixture was allowed to reach room temperature. The mixture was filtered (Hyflo) and the filtrate was exhaustively concentrated *in vacuo* after which the residue was washed with diethylether. Yield: 0.95 g (100%) of III-H. TosOH.

Step 1 (scheme iv):

[0051] 42 g (0.22 mol) of the nitroquinoline were suspended in 1000 ml of 96% EtOH. To the latter solution 19.5 g of 10% Pt-C/H₂O was added. While stirring, the mixture was hydrogenated under a pressure of 4 atmospheres eventually, in the beginning of the reaction the consumption of hydrogen is so fast that the pressure could not reach 4 atmospheres instantly. For 2 days the reaction was continued, during the nights the mixture was put under a nitrogen atmosphere. After this period the catalyst was removed by filtration and the filtrate concentrated *in vacuo* leaving 35.5 g of crude product which was subjected to column chromatography (SiO₂, eluent: CH₂Cl₂/MeOH = 99/1) yielding 25 g (70%) of the desired product.

Step 2 (scheme iv):

[0052] This step is similar to step 2 described in scheme ii.

Step 3 (scheme iv):

[0053] 0.7 g (1.7 mmol) of the N-tosyl homopiperazine was dissolved in 20 ml of concentrated HCl after which the mixture was refluxed for 16 hrs. After the reaction mixture had reached room temperature, it was poured into an aqueous K₂CO₃ solution. The basic mixture was extracted with EtOAc after which the organic fraction was dried on MgSO₄. After removal of the drying agent and evaporation of the solvent *in vacuo*, the residue was subjected to flash column chromatography (SiO₂, eluent: CH₂Cl₂/MeOH/NH₄OH(25%,aq) = 92/7.5/0.5) which yielded 0.4 g (96%) of IX-H as a brownish oil.

Step 1 (scheme vi):

[0054] 1.2 g (3.6 mmol) of the N-benzyl-piperazine derivative (which can be prepared analogously to the procedure described for the synthesis of 1-[5-(1,4-benzodioxanyl)]-*trans*-3,5-dimethyl-piperazine, see EP 0189612) was dissolved in 50 ml of EtOAc/MeOH = 1/1, after which a catalytic amount of 10% Pd-C was added. The solution was agitated under atmospheric H₂-pressure for 60 hrs. After the latter period the catalyst was removed by filtration, the filtrate concentrated *in vacuo*, after which the residue was subjected to flash column chromatography (SiO₂, eluent: CH₂Cl₂/MeOH/NH₄OH(25%,aq) = 92/7.5/0.5) yielding 0.7 g (80%) of XV-H as a yellow oil which solidified on standing.

Step 1 (scheme vii):

[0055] 0.5 g (2.1 mmol) of the oxime was added to 5 g of polyphosphoric acid which was heated at 110 °C. After 0.5 hrs, the warm (T < 80 °C) reaction mixture was poured into saturated aqueous NaHCO₃ solution. After a while extraction was performed with EtOAc after which the organic fraction was dried on Na₂SO₄. After removal of the drying agent and evaporation of the solvent *in vacuo*, 0.42 g (84%) of solid azepinone was left.

Step 2 (scheme vii):

[0056] 100 ml of toluene were flushed with N₂. 0.96 g (4 mmol) of the azepinone, 2.75 g (32 mmol, 8 eq.) of piperazine, 5.2 g (36 mmol, 9 eq.) of NaOtBu, 0.04 g (0.04 mmol, 0.01 eq.) of Pd₂(dba)₃ and 0.082 g (0.12 mmol, 0.03 eq.) of (R)-(+)-BINAP were added to the toluene. The mixture was brought to a temperature of 80 °C for 16 hrs. After cooling the solution was concentrated *in vacuo*, after which the residue was subjected to flash column chromatography (SiO₂, eluent: CH₂Cl₂/MeOH/NH₄OH(25%,aq) = 92/7.5/0.5) yielding 0.95 g of reddish material. The latter was treated with aqueous 2 M NaOH after which extraction took place with CH₂Cl₂. The organic fraction was washed with water and dried on Na₂SO₄ and a little charcoal was added. After removal of the drying agent and charcoal by filtration and evaporation of the solvent *in vacuo*, 0.56 g (57%) of light yellow XVII-H was isolated.

Intermediate used in Example 3

[0057] For the synthesis of A23, O-mesyl-N-benzyloxycarbonyl-(R)-alaninol was needed, the synthesis of this intermediate was performed as follows:

2.0 g (8.4 mmol) of N-benzyloxycarbonyl-(R)-alanine methyl ester were dissolved in 20 ml of MeOH, after which 0.96 g (25 mmol) of NaBH₄ was added carefully (foam). Stirring was continued for 1 hr at room temperature after which the reaction mixture was acidified (2 M HCl) to about pH 2. EtOAc was added and after agitation the organic fraction was separated and dried on Na₂SO₄. After removal of the drying agent and the solvent *in vacuo*, leaving 1.8 g of a colorless oil, containing the N-benzyloxycarbonyl-(R)-alaninol. The latter compound was transformed into its corresponding mesylate by the standard treatment with tri-ethyl-amine in CH₂Cl₂ at -5°C after which mesylchloride is added. After work-up 74% of the corresponding mesylate could be isolated as a white solid.

Intermediates Q-Cl and Q-Br:

[0058] Q3-Cl was prepared from commercially available 3-bromo-2-methyl-1-chloro-propane and *para*-fluorophenol: 2.45 g (106.5 mmol) of Na was reacted with 75 ml of absolute EtOH after which, while stirring, 10.0 g (89 mmol) of *para*-fluorophenol was added. The resulting solution was added dropwise to a warm solution of 45.8 g (267 mmol, 3 eq.) of 3-bromo-2-methyl-1-chloro-propane in about 20 ml of absolute EtOH. Stirring at reflux temperature was continued for 40 hrs. After cooling, the precipitate was removed by filtration, subsequently the filtrate was concentrated *in vacuo* and the residue treated with 2 M NaOH. The resulting solution was extracted with Et₂O. The combined organic fractions were washed with water and dried on Na₂SO₄. After removal of the drying agent and the solvent *in vacuo*, 26 g of a yellow oil was left. Dry chromatography (SiO₂, eluent: petroleum benzin) yielded 9.9 g (54%) of Q3-Cl. This amount was contaminated (ca. 30%) with the HCl eliminated side product of Q3-Cl. However, this batch was well suited for reaction with the described piperazines (see scheme A1).

[0059] Q9-Br was prepared in a Friedel-Craft reaction from *racemic* 4-bromo-2-methyl-butyryl bromide (for preparation see E.E. Ziegler et al., *J. Am. Chem. Soc.*, 112(1990)2755) and fluorobenzene:

While stirring at room temperature and under a nitrogen atmosphere, 6.8 g (51 mmol) of AlCl₃ were suspended in 70 ml of 1,2-dichloro-ethane. Then 11.5 g (47 mmol) of *racemic* 4-bromo-2-methyl-butyryl bromide were added dropwise to the mixture. After 10 minutes the mixture was brought to 15 °C after which 14 ml (149 mmol, 3.2 eq.) of fluorobenzene was added dropwise. No change in temperature occurred. Stirring was continued for 18 hrs at room temperature, after which the reaction mixture was worked up carefully with water (temperature was kept below 40 °C). An extra amount of 1,2-dichloro-ethane was added. The biphasic system was separated and the organic layer was washed with water. Subsequently the organic layer was dried on Na₂SO₄. After removal of the drying agent and the solvent *in vacuo*, 10.7 g (88%) of Q9-Br resulted as a yellow oil. This almost pure oil was used for the reactions with the described piperazines (see scheme A1).

[0060] Q10-Br was prepared in a two-step synthesis; step 1: commercially available (S)-2-oxo-4-methyl-tetrahydrofuran was reacted with PBr₃ according to the procedure described by E.E. Ziegler et al., *J. Am. Chem. Soc.*, 112(1990)2755, giving (S)-4-bromo-3-methyl-butyryl bromide in 39% yield. Step 2: the latter compound was reacted with fluorobenzene in a Friedel-Craft reaction according to the procedure given for Q9-Br yielding 78% of the wanted product (*vide supra*). The obtained Q10-Br appeared not to be a good alkylating agent, therefore the diethylketal was

prepared by treating Q10-Br with tri-ethoxymethane: 1.0 g (3.9 mmol) of Q10-Br was dissolved together with 1.14 g (7.72 mmol) of ethylorthoformate ($\text{CH}_3\text{CH}_2\text{O}$)₃CH in 1.0 ml of absolute ethanol. After 5 minutes 1 small drip of 5 M H_2SO_4 was added. Stirring was continued for 16 hrs at room temperature after which the reaction mixture was concentrated *in vacuo*, leaving a dark residue of crude diethylketal of Q10-Br. The latter preparation was used without further purification for the synthesis of compound A20.

Q-OH:

[0061] Q2-OH was prepared from $\text{NaOCH}_2\text{CH}_2\text{OH}$ and p-fluorobenzylbromide:

2.75 g (0.12) mol of Na was reacted with an ample amount of absolute methanol. After the reaction had been completed, the excess MeOH was removed *in vacuo*. To the remaining white solid 24 ml (2.75 g, 0.4 mol) of ethyleneglycol was added after which the temperature was raised to 170 °C. After 3 hrs the reaction mixture was allowed to reach 80 °C, at which temperature the liberated MeOH was removed *in vacuo*. Then, still at 80-90 °C, 23.7 g (0.125 mol) of p-fluorobenzylbromide was added dropwise to the reaction mixture, after the addition was completed stirring and heating at 130 °C were continued for three hours. After reaching room temperature, the reaction mixture was poured into water. The latter mixture was extracted with EtOAc, and the combined organic fractions were washed with water and dried on MgSO_4 . After removal of the drying agent and the solvent *in vacuo*, 21.3 g of an oily residue was left. Chromatography (silicagel, eluent: Et_2O /petroleum benzin 1/1) yielded 16.6 g (78%) of pure product Q2-OH.

[0062] Q4-OH was prepared from 3-hydroxy-1-butanol in three steps according to the procedure described in EP89009149: the first step being the protection of the primary alcohol group with the *tert.* butylcarbonyl moiety, the second step being a Mitsunobu reaction between the latter compound and *para*-fluorophenol. The third step, the deprotection of the primary hydroxy group, gave the desired Q4-OH in 32% overall yield.

[0063] Q5-OH was prepared similarly to the procedure described in H. Haubenstock et al., *J. Am. Chem. Soc.*, 84(1962)2372.

[0064] Q6-OH was prepared from commercially available (S)-3-bromo-2-methyl-1-propanol and *para*-fluorophenol:

[0065] 7.56 g (49.4 mmol) of (S)-3-bromo-2-methyl-1-propanol and 11 g (98 mmol) of *para*-fluorophenol were dissolved in 150 ml of acetone after which 18 g (130 mmol) of powdered K_2CO_3 were added. The reaction mixture was brought to refluxing temperature for a period of 24 hrs. After the reaction mixture had reached room temperature, the solvent was removed *in vacuo* leaving a residu which was dissolved in ethyl acetate/water. The organic layer was washed subsequently with 2 N NaOH and water (2x), after which the solution was dried on MgSO_4 . After subsequent removal of the drying agent and the solvent, the residu was subjected to flash chromatography (SiO_2 , eluent: petroleum benzin/methyl-*tert.*-butyl ether 2/1) which eventually yielded 4.65 g (25.1 mmol, 51%) of a colorless oil consisting of Q6-OH.

[0066] Q7-OH was prepared from commercially available (R)-3-bromo-2-methyl-1-propanol and *para*-fluorophenol in the same way as Q6-OH (*vide supra*).

[0067] The above described Q-OH were converted into their corresponding mesylates and tosylates by standard procedures, e.g. $\text{MsCl}/\text{Et}_3\text{N}$ and $\text{TosCl}/\text{pyridin}$ respectively. See also table A1 (*vide infra*).

[0068] Q11 and Q12 are introduced in the compounds as described in scheme A2 (*vide infra*).

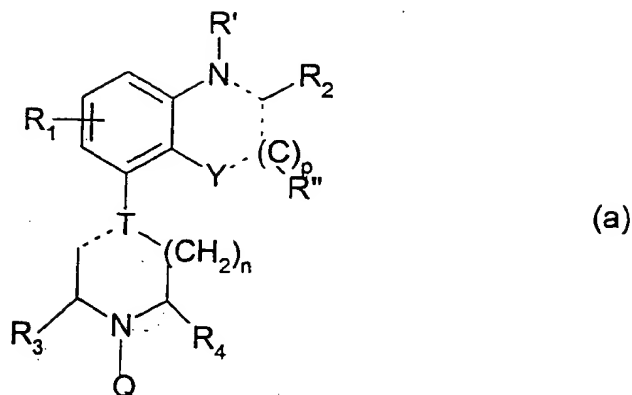
[0069] Q13, Q14 and Q15 are introduced in the compounds as described in scheme B1 (*vide infra*).

[0070] Q16-32 are introduced in the compounds as described in scheme C1 (*vide infra*).

Q17 can also be introduced as described in scheme D1.

Claims

1. Compounds having formula (a)



wherein

- R_1 is hydrogen or fluoro,
- R' is H or C_{1-4} -alkyl,
- R_2 is H, C_{1-4} -alkyl or an oxo group, or R' and R_2 together represent a bond,
- R'' is H or C_{1-4} -alkyl, and the dotted lines can represent a single or double bond,
- p has the value 0-2,
- Y represents C, O, N or S,
- T represent N or C,
- R_3 and R_4 independently are hydrogen or C_{1-4} -alkyl,
- n has the value 1 or 2,
- Q is a group of the formula $-CH_2-C(R_5R_6)-Z-R_7$ wherein R_5 and R_6 represent H or C_{1-7} -alkyl, C_{1-3} -alkylphenyl, Z represents $-C(R_8R_9)-O-$, $-C(R_8R_9)-C(=O)-$, $-C(R_8R_9)-C(=NOR_{10})-$, $-NH-C(=O)-$ or $-O-CH_2-$, wherein R_8 - R_{10} represent H or C_{1-4} -alkyl, and R_7 is a 5- or 6-membered cyclic group, aromatic group or hetero-aromatic group, or the 1- or 2-adamantyl group, which group R_7 can substituted with $O-C_{1-4}$ -alkyl, CN, halogen or C_{1-4} -alkyl,

with the proviso that R_7 cannot be 1-alkylcycloalkyl, and that compounds wherein Z is the group $-NH-C(=O)-$ and $R_5=R_6=H$, T is nitrogen, and the bicyclic group is 1,4-benzoxazin-8-yl, quinoxalin-5-yl, quinolin-5-yl, indol-4-yl, benzoxazol-7-yl, benzimidazol-4-yl, benzothiazol-7-yl are not included, and salts thereof.

2. Compounds as claimed in claim 1, wherein T represents nitrogen, R' is hydrogen and the other symbols have the meaning given in claim 1.
3. Compounds as claimed in claim 1, wherein Y is carbon and T is nitrogen, $p=1$, $n=1$, R_1 , R' , R_2 , R'' , R_3 and R_4 are hydrogen, the dotted lines are single bonds, and Q is a group of the formula $-CH_2-C(R_5R_6)-Z-R_7$ wherein R_5 and R_6 represent H, C_{1-4} -alkyl or benzyl, Z is $-C(R_8R_9)-C(=O)-$, $-C(R_8R_9)-O$ or $-NH-C(=O)-$, wherein R_8 and R_9 represent hydrogen or methyl, and R_7 is phenyl optionally substituted with halogen, CN, CH_3 or OCH_3 .
4. Pharmaceutical compositions which contain at least one compound as claimed in claim 1 as an active component.
5. Method of preparing compositions for treating CNS-disorders, characterized in that a compound as claimed in claim 1 is brought into form suitable for administration to a patient.
6. Method of treating CNS-disorders, characterized in that a compound as claimed in claim 1 is used.
7. Method of treating schizophrenia, characterized in that a compound as claimed in claim 1 is used.
8. A method of preparing piperazine and piperidine derivatives, characterized in that a compound as claimed in claim 1 is prepared in a manner known for analogous compounds.



European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 98 20 2832

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
P, Y	WO 97 36893 A (DUPHAR INT RES ; FEENSTRA ROELOF WILLEM (NL); KRUSE CORNELIS GERRIT) 9 October 1997 * claim 1 *	1-8	C07D263/58 C07D209/34 A61K31/42 A61K31/38 A61K31/47
X	EP 0 169 148 A (ROUSSEL-UCLAF) 22 January 1986 see claim 1 formula, specifically the definitions of Z * claim 1; example 30 *	1-8	C07D209/08 C07D265/36 C07D215/227 C07D279/16 C07D401/12 C07D409/12
Y	EP 0 785 195 A (AMERICAN HOME FOOD PRODUCTS INC) 23 July 1997 see the whole document	1-8	
Y	US 5 519 025 A (AMERICAN HOME RPRODUCTS) 21 May 1996 see the formula and column 3, lines 1-10 * example 3 *	1-8	
Y	WO 96 03400 A (PFIZER ; MACOR JOHN EUGENE (US)) 8 February 1996 * claim 1 *	1-8	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	US 5 486 518 A (AMERICAN HOME PRODUCTS) 23 January 1996 see the definitions of R2, R3 and R1	1-8	C07D A61K
D, Y	EP 0 650 964 A (DUPHAT INTERNATIONAL RESEARCH) 3 May 1995 see the whole document	1-8	
Y	WO 95 02592 A (WYETH JOHN & BROTHER LTD ; AMERICAN HOME PROD (US); CLIFFE IAN ANTH) 26 January 1995 * claim 1 *	1-8	
The present search report has been drawn up for all claims			
Place of search MUNICH		Date of completion of the search 3 December 1998	Examiner Gettins, M
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document</p> <p>T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons & member of the same patent family, corresponding document</p>			

EPO FORM 1600 03 82 (04/01)



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EUROPEAN SEARCH REPORT

Application Number
EP 98 20 2832

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<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

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